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ORIGINAL ARTICLE

Carotid Intima-Media Thickness and Metabolic Complications in Children with HIV on Antiretroviral Therapy: A Cross-Sectional Study

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Abstract

Objectives To evaluate carotid intima media thickness (CIMT) in children with Human immunodeficiency virus (HIV) on anti-retroviral therapy (ART) and in controls. Also, to compare body mass index (BMI), body fat percentage, skin-fold thickness (SFT), waist-to-height ratio (WHtR), lipid profile, blood pressure, lipodystrophy syndrome (LDS), non-alcoholic fatty liver disease (NAFLD) in children with HIV and in controls and to determine association between lipid profile, LDS, liver amino-transferases, NAFLD, BMI, body fat percentage, SFT, WHtR and CIMT.

Methods This cross-sectional study was done in 7 to 12 y old children attending the ART clinic and receiving ART for ≥6 mo according to 2018 National Aids Control Organization (NACO) guidelines. Thirty age and gender matched controls were enrolled from the pediatrics OPD. Weight, height, BMI, waist circumference, skin fold thickness and blood pressure were recorded. Lipid profile, liver amino-transferases, USG abdomen and CIMT were done with prior appointment.

Results The present study had 43% females and 57% males (mean age of 9.33 ± 1.65 y). All cases were on combination ART (mean treatment duration: 59.1 mo). CIMT was significantly increased in cases as compared to controls 0.481 ± 0.087 mm vs. 0.418 ± 0.072 mm ($p = 0.003$). However, CIMT did not correlate with any other parameter. Cases had significantly higher body fat percentage (17% vs. 13.15%), systolic blood pressure (SBP), SFT, total cholesterol (TC) and low density lipoprotein- cholesterol (LDL-C) as compared to controls. NAFLD was seen in 3 cases (1%), lipohypertrophy in 7 (23%) cases and 5 (16%) controls.

Conclusions Children with HIV on ART have significantly higher CIMT and increased metabolic abnormalities.

Keywords Carotid intima media thickness (CIMT) · Anti-retroviral therapy (ART) · Metabolic profile

Introduction

According to the India Human immunodeficiency virus (HIV) estimates 2020; 81,430 children were living with HIV [1]. Due to improved antiretroviral therapy (ART) coverage, the life expectancy has improved and these children continue to live longer. Thus, these children are predisposed to long term metabolic complications associated with ART [2, 3].

Long standing HIV-related dyslipidemia causes changes in the vasculature. Thickening in vessel wall has been extensively reported in the adult population living with HIV [4]. Whether similar effects are also seen in pediatric population with HIV has still not been well studied. Dyslipidemia leads to increase in carotid intima media thickness (CIMT), which is a valuable surrogate marker of cardiovascular disease [5]. Few Indian studies showed high prevalence of dyslipidemia and lipodystrophy syndrome in children living with HIV (CLHIV) [6–10] but to the best of authors' knowledge no study has been done till date in Indian children with HIV to see how the CIMT is affected in CLHIV.

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Material and Methods

This cross-sectional study was done over 19 mo from January 2021 to August 2022 in a tertiary care hospital of India. Recruitment was done from the ART clinic. Approvals of the ethical committee of the institute and Delhi State Aids Control Society were obtained. Written informed consent was obtained from the participating child's parents/guardian/caregiver. Assent was taken in children aged 7–12 y.

In a previous similar study by Chanthong et al., CIMT value was 0.373 mm. Taking the median and interquartile range (IQR) as 0.373 (0.284–0.451), to estimate relative difference of 10% on either side, $\alpha = 5\%$, a sample of 20 cases was required [11]. The sample size was calculated as per methods explained by Hozo et al., using median and IQR [12]. The authors enrolled 30 cases and 30 age & gender matched controls.

All children aged between 7 and 12 y attending the ART clinic and receiving antiretroviral therapy for ≥ 6 mo according to 2018 National AIDS Control Organization (NACO) guidelines were included in the study.

Age and gender matched controls were enrolled from those attending the pediatric OPD for minor illnesses.

Weight, height, waist circumference, skin-fold thickness over triceps and systolic and diastolic blood pressures were measured by single trained observer using standard methods. Waist-to-height ratio (WHtR) and body mass index (BMI) was calculated. For calculating the z-score, WHO Anthro software version 3.2.2 (World Health Organization, available from http://www.who.int/childgrowth/en) was used. The z-score for weight for age, height for age and BMI z-scores were calculated using this application.

CIMT was measured by color Doppler ultrasound by a radiologist using available ultrasound machine with linear probe (7–12 MHz). Patient was laid down supine with the head slightly tilted contralateral to the side being examined. The far wall of the left and right common carotid artery was scanned 1 cm below the carotid bulb over a length of 1 cm in the sagittal plane. Hypoechoic area between intima and externa was measured on both sides and average was recorded. CIMT was measured in millimetres. Sex-specific percentile curve for carotid intima-media thickness (CIMT, mm) were used [13].

Assessment of fat redistribution was done and was clinically classified as either peripheral lipoatrophy or central lipohypertrophy or combined type [14]. Triceps skin-fold thickness (TSFT) was measured from behind by taking skin pinch between index finger and thumb, about 1 cm above the midpoint over the triceps muscle. TSFT was measured using skin-fold calliper manufactured by Baseline, India.

Detection of non-alcoholic fatty liver disease (NAFLD) was done by USG of right upper-abdomen performed on BPL Alpinion Model ECUBE-7 by using curvilinear probe (3–5 MHz). Liver size was measured - the maximum cephalocaudal dimension in the mid-clavicular line. Liver margins, any space occupying lesion, echotexture was looked for. Portal vein and biliary radicles were noted. The ultrasonographic steatosis score was defined as - no steatosis (grade 0), mild steatosis (grade 1), moderate steatosis (grade 2) and severe steatosis (grade 3).

Body fat percentage was measured by the bioelectrical impedance (BIA) monitor by using Tanita BC148MA segmental body composition analyser. BIA measurements were made adhering to manufacturer's guidelines and measurement frequency of 50 Hz. Height, gender and age was entered manually, while weight was automatically recorded using 0.5 kg as an adjustment for clothing weight in all subjects.

Blood sampling for high density lipoprotein-cholesterol (HDL-C), low density lipoprotein- cholesterol (LDL-C), total cholesterol (TC), and triglycerides (TG) and serum transaminases [aspartate aminotransferase (AST) and alanine transaminase (ALT)] were done later with prior appointment (after 12 h of fasting) using UniCelDxC 600 Autoanalyser. USG abdomen and CIMT assessment were also done in the same visit.

Data was entered in MS Excel sheet and was analysed using IBM SPSS 20.0. CIMT was compared using Student's t-test. Lipid profile, CIMT, BMI, body fat percentage, TSFT, WHtR were expressed as mean/median (standard deviation/IQR), NAFLD and lipodystrophy syndrome as frequency (%). Lipodystrophy syndrome and NAFLD were compared using chi-square test. CIMT, lipid profile, AST, ALT, WHtR, BMI were compared using Student's t-test. *P* value of <0.05 was considered significant. Pearson's correlation coefficients were calculated.

Results

Thirty children living with HIV on ART (cases) and 30 controls (age and gender matched) were enrolled. All participants were between 7 to 12 y of age with mean age of 9.33 ± 1.65 y (Median 9 y: IQR 8–11). The authors recruited 13 females and 17 males in both groups. Children living with HIV were shorter in height, had a higher BMI, waist circumference and waist-to-height ratio (Table 1) but these differences were not statistically significant. None of the cases or controls were underweight (z-score <-2). However, stunting (z-score <-2) was seen in 9 cases (5 boys and 4 girls), but none of the controls had stunting and this difference was significant ($p = 0.002$). Increased BMI was present only in 2 cases, (case 1: z-score >+2, case 2: z-score >+1). None of the cases or controls had BMI with z-score <-2. Among

Table 1 Comparison of baseline characteristics between cases and controls

	Cases (n = 30)		Controls (n = 30)		*P* value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Weight (kg)	25.88 ± 11.67	21.5 (15.42-27.58)	25.03 ± 6.43	23.9 (19.16-28.64)	0.821
Height (cm)	125.42 ± 14.29	123 (113.75-132.25)	130.86 ± 12.33	132.25 (122-142.5)	0.118
BMI (kg/m^2)	15.67 ± 3.76	14.6 (12.78-16.42)	14.57 ± 1.52	14.5 (13.5-15.46)	0.141
Waist circumference (cm)	56.05 ± 9.88	54.75 (50.7-58.8)	55.80 ± 6.39	55 (52.05-57.95)	0.908
WHtR	0.44 ± 0.09	0.45 (0.42-0.49)	0.42 ± 0.03	0.43 (0.41-0.46)	0.444

BMI Body mass index, *WHtR* Waist-to-height ratio

$p < 0.05$ is statistically significant

cases, 10 cases each were in Tanner stage I & II respectively (33.3%), 9 were stage III (30%) and 1 was in stage IV (3.4%). In controls 11 participants were in Tanner stage I (36.6%), 15 in stage II (50%) and 4 in stage III (13.4%). None of the controls were in stage IV of sexual maturity rating (SMR).

All the cases were on combination ART with 2 nucleotide reverse transcriptase inhibitors (NRTIs) along with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Among NRTIs - 29 cases were on lamivudine (13 on zidovudine, 15 on abacavir and 1 on tenofovir). The third most common drug combination was NNRTI, 26 patients were on NNRTIs (19 on efavirenz and 7 on nevirapine); 4 were on PIs (3 on Lpv/rtv and 1 on combination of Lpv/rtv with atazanavir). The mean duration of treatment with ART was 59.1 mo.

CLHIV had significantly increased systolic blood pressure (SBP) but there was no significant difference in diastolic blood pressure (DBP) (Table 2). Six cases had elevated SBP [≥90th percentile to <95th percentile as per American Academy of Pediatrics (AAP) 2017 BP charts] and 4 had either stage I or stage II hypertension (≥95th percentile). None among the controls had elevated SBP or hypertension.

CLHIV also had significantly higher body fat percentages and higher TSFT. Two cases had TSFT >70th percentile of the Indian reference standards [15], whereas none of the controls had raised TSFT values.

TC and LDL-C were also significantly raised in cases when compared to controls. Nine (30%) cases and 2 (6.6%) controls had raised TC. Raised LDL-C was seen in 3 cases and 1 control. Low HDL-C were found in 11 (36.6%) cases and 8 (26.6%) controls. Fourteen (46.6%) cases and 9 (30%) controls had elevated TG. Three cases had NAFLD ($p = 0.237$). Seven cases and 5 controls had lipodystrophy (all being lipohypertrophy) but the difference was not significant ($p = 0.803$).

The mean, right and left CIMT was significantly more in cases (Fig. 1; Table 3). When 50th percentile of reference values was taken as normal; 16 cases (53%) and 8 controls had increased CIMT ($p = 0.064$) [13].

There was no significant correlation between in BMI, body fat percentage, skin-fold thickness, waist-to-height

Table 2 Comparison of outcome parameters between cases and controls

	Cases (n = 30)		Controls (n = 30)		*P* value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
SBP (mm Hg)	105.13 ± 9.79	103.5 (96.5-110.5)	99.97 ± 6.03	100 (96.5-103.5)	0.018*
DBP (mm Hg)	65.67 ± 7.23	67 (61.5-72.5)	63.13 ± 5.92	60 (55.5-64.5)	0.32
Skin-fold thickness (mm)	8.51 ± 3.48	7.25 (6.19-8.32)	6.39 ± 0.94	6 (5.69-6.32)	0.002*
Body fat percentage (%)	17.01 ± 5.82	15.25 (12.3-18.2)	13.15 ± 3.73	13.1 (10.8-15.4)	0.003*
TC (mg/dl)	177.23 ± 36.37	178.5 (165-204)	147.27 ± 29.28	139.5 (113-239)	<0.001*
LDL-C (mg/dl)	110.28 ± 31.03	103.6 (98.1-148.9)	76.88 ± 29.73	74.95 (38.2-190.2)	0.001*
HDL-C (mg/dl)	45.53 ± 12.13	50.5 (42-46)	44.37 ± 13.60	42 (37-77)	0.727
TG (mg/dl)	107.13 ± 37.72	106.5 (114-133)	96.87 ± 51.57	83 (77-246)	0.382
AST (IU/L)	34.03 ± 7.61	32.5 (33-40)	31.86 ± 9.21	32.5 (25-43)	0.325
ALT (IU/L)	26.13 ± 11.73	21 (26-54)	22.66 ± 9.26	20 (24-35)	0.209

ALT Alanine transaminase, *AST* Aspartate aminotransferase, *DBP* Diastolic blood pressure, *HDL-C* High density lipoprotein-cholesterol, *LDL-C* Low density lipoprotein-cholesterol, *SBP* Systolic blood pressure, *TC* Total cholesterol, *TG* Triglycerides

*$p < 0.05$ is statistically significant

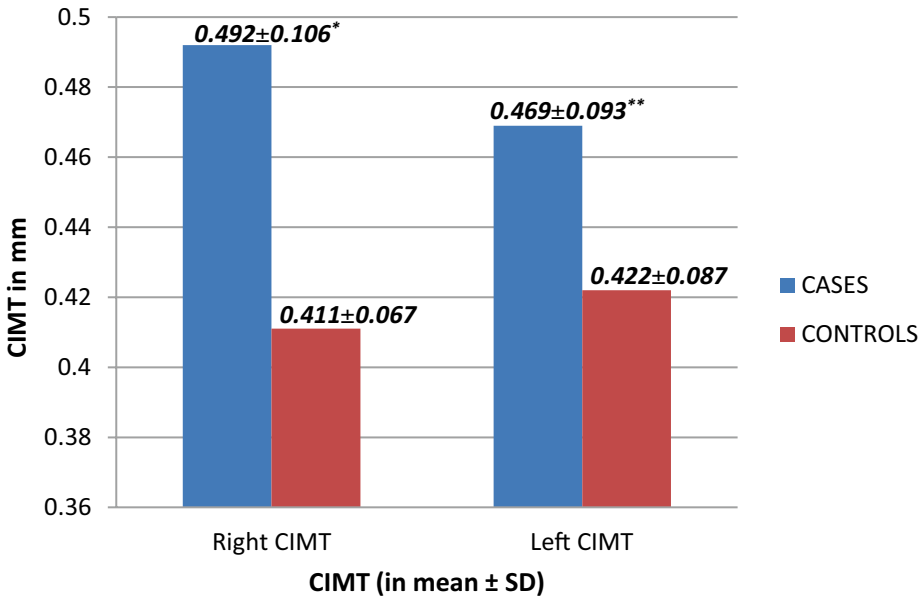

Fig. 1 Comparison of left CIMT and right CIMT between cases and controls. *p = <0.001, **p = 0.048. *CIMT* Carotid intima media thickness

ratio, SBP, DBP, total cholesterol, LDL-C, HDL-C, TG, AST, ALT, occurrence of lipodystrophy/ NAFLD and CIMT.

Discussion

The present study showed that the mean weight, height, WHtR and BMI of CLHIV were comparable to healthy controls. CLHIV had a significantly higher percentage of total body fat when compared to the controls (17% vs. 13.15%, $p = 0.003$). This is similar to the study done by Sharma et al. wherein, they found that young females (children and adolescents) with HIV who had been perinatally infected with HIV had higher rates of yearly increment of body fat percentage (estimate = 1.212 percent per year, $p < 0.001$) as compared to HIV negative controls [16].

The present cases also had a significantly increased triceps skin-fold thickness. Arpadi et al., found that HIV-infected children who were on Lpv/rtv regimen had significantly higher skin-fold thickness as compared to those who were on nevirapine based regimen [17]. However, in the study done by Musiime et al., HIV-infected children on ART had thinner biceps, triceps and total skin-fold thickness when compared to ART-naïve HIV-infected children as well as controls [18].

In the present study, the authors also observed significantly higher SBP in cases but there was no significant difference in DBP. This is similar to the study done by McComsey et al. [19]. However, Bonnet et al. found no difference in SBP/DBP [20]. CLHIV also had a significantly higher TC and LDL-C as compared to controls. Kumar et al., found raised TC, LDL-C and HDL-C in ART-experienced CLHIV as compared to ART-naïve CLHIV [9]. Similar results were also observed by Mandal et al. [7]. Parakh et al., in northern India also found higher values of total cholesterol and HDL-C in highly active antiretroviral therapy (HAART)–experienced children with the total cholesterol value being significantly higher [10]. Similar to the present study, Charakida et al., also found raised TC and triglycerides (significantly raised) but lower HDL-C in CLHIV as compared to healthy controls, whereas significantly higher level of TC and triglycerides was seen by McComsey et al.

Table 3 Comparison of the mean of left and right CIMT between cases and controls

	Cases (n = 30)		Controls (n = 30)		*P* value	95% Confidence Interval
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)		
Mean CIMT (mm)	0.481 (0.087)	0.475 (0.441-0.459)	0.418 (0.072)	0.4 (0.413-0.437)	0.003*	0.021-0.104

CIMT Carotid intima media thickness

*p <0.05 is statistically significant

[19, 21]. Chanthong et al., found significantly raised triglycerides and significantly reduced HDL-C in cases but no significant difference was seen in total cholesterol and LDL-C [11]. The higher cholesterol values seen in present study are in concordance with the higher cholesterol values seen in ART experienced children living with HIV in the other Indian studies. The HIV requires endogenous cholesterol for its normal pathogenesis and infectivity and in the pursuit for this, hampers cholesterol efflux from macrophages which leads to lipid abnormalities [22]. HIV-infection promotes a state of sustained inflammation, and elevated lipids are due to the response of rise in pro-inflammatory markers.

Three cases had NAFLD in the form of mild steatosis and none of the healthy controls had NAFLD, however, this difference was not significant. In a study done by Shah in India for adverse effects of ART in HIV-infected children, hepatotoxicity was the most common and steatosis was the least common adverse effect seen [23]. Fatty liver disease in HIV has been associated with multiple factors, including factors associated with NAFLD in the general population such as gender, obesity, insulin resistance, and hypertriglyceridemia, and with HIV-related factors including ART and lipodystrophy.

The authors also observed lipodystrophy in 7 cases (23%) and 5 controls (16%), all having lipohypertrophy but the difference was not significant. All 7 cases were on NNRTIs and none received any PI or stavudine. Indian studies showed prevalence of lipodystrophy ranging from 33.7% [10] to 47.7% [9] to 80.2% [7], wherein a significant number of patients in their studies were being treated with stavudine-based therapy. In the current study, authors did not observe any lipoatrophy as none of the participants were on stavudine-based ART. Stavudine based regimens are known to cause the maximum lipoatrophy.

In the current study, right, left and mean CIMT values were significantly higher in cases as compared to controls. These findings are in concordance with the study done by Charakida et al.; mean IMT value was 0.6 mm in HIV-infected children as compared to 0.47 mm in controls and this difference was statistically significant ($p = <0.001$) [21]. McComsey et al., also found significantly higher mean value of both right and left CIMT in HIV-infected children than in controls [19]. Similar results were observed by de Lima et al., [24] and Marsico et al., [25]. The HIV binds to macrophages and inhibits the normal cholesterol efflux from it, thus reducing the ability to export excessive cholesterol. This causes a virus mediated switch of cholesterol transport from normal to virus-controlled transport. This inhibition leads to excessive accumulation of cholesterol in the HIV-infected macrophages resulting in formation of foam cells which causes endothelial deposition and plaque formation and subsequently, atherosclerosis [22].

The authors found a negative correlation of mean CIMT with LDL-C, but there was no significant correlation of either left CIMT or right CIMT with LDL-C. They could not explain the reason for this correlation. CIMT had no correlation with any of the other metabolic parameters.

The presence of elevated values of body fat percentage, CIMT and SBP in HIV-infected children may be indicative of the changing trend towards overweight or obesity in the urban population of India. This may be partly related to the ready availability of high fat content food/junk food and decreased physical activity. Moreover; this study was conducted during the COVID pandemic (including many months of strict lockdown), this may have impacted these parameters due to change in lifestyle.

There were certain limitations of the present study. The study population was small and hence not adequately representative of the population. In the present study authors used bioelectrical impedance to measure body fat percentage which is a crude and approximate measure. It is not the absolute measure of the body fat. For assessing fat redistribution, they used clinical markers of lipodystrophy and waist circumference. These are surrogate markers and it may not reliably detect visceral fat deposition. More sensitive techniques like DEXA or MRI would have given better results regarding fat distribution after HIV infection or initiation of ART. In the present study authors have compared HIV-infected children who were already on ART with healthy controls. This study design does not elucidate that the metabolic derangements found in HIV-infected children are due to the effect of HIV infection per se or the effect of antiretroviral drugs.

Since HIV-infected children will take life-long ART, it is imperative to minimize the metabolic derangements and cardiovascular risks right from the childhood. Early detection of dyslipidemia and atherosclerotic risk by non-invasive techniques like CIMT measurement can identify at-risk patients who could be potential targets of early intervention.

Conclusions

When compared to the healthy control group; the mean, right and left CIMT were significantly higher in the children with HIV on antiretroviral therapy. These children also suffer from other metabolic abnormalities which may predispose them for increased future cardiovascular risks. Thus, authors conclude that children on ART have higher CIMT and an increased cardiovascular risk.

The authors recommend large cohort studies to find out if this increased cardiovascular risk is because of HIV

infection per se or is it because of the ART, and also to explore preventive therapies/strategies to reduce these risks for improved survival and quality of life in these children.

Authors' Contributions KM: manuscript preparation, study sample collection and analysis of data; DH: study design and analysis and discussion of results; SG: analysis and discussion of results; VR: radiological evaluation of patients. DH will act as guarantor for this manuscript.

Declarations

Conflict of Interest None.

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